

# Encephalitis and Viral Persistence



**Bryan Smith, MD. Staff Clinician, NINDS  
and**

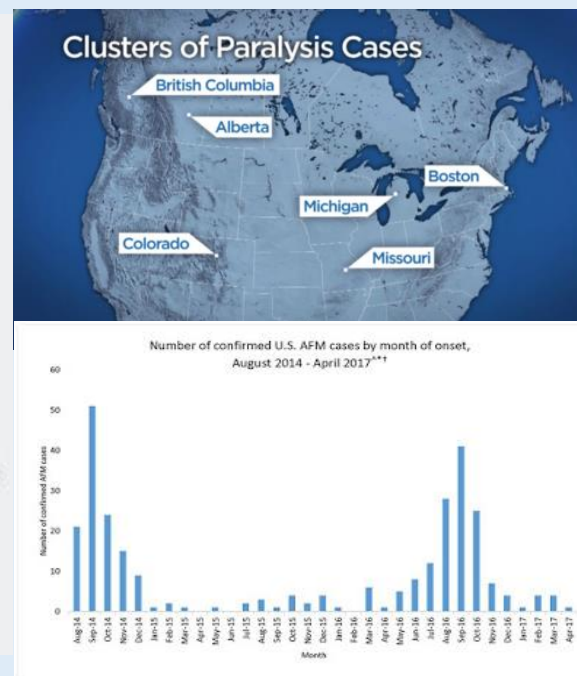
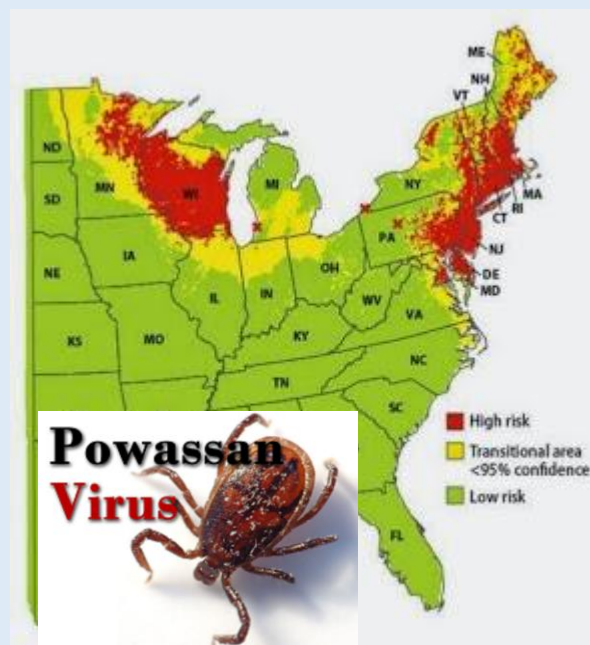
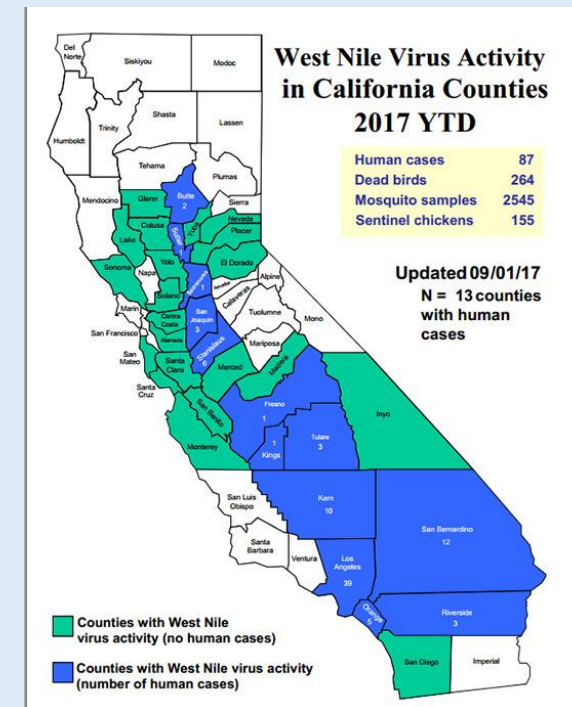
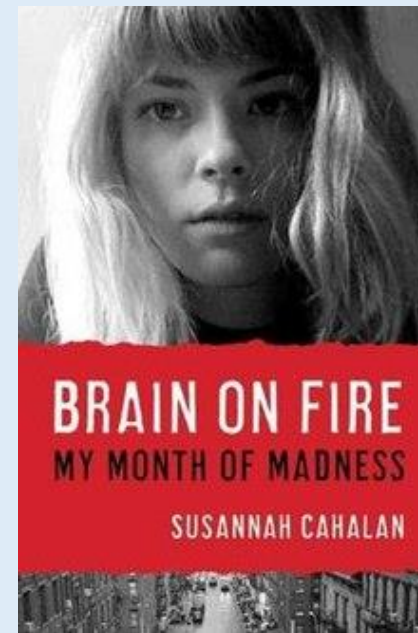
**Avi Nath, MD. Clinical Director, NINDS**

**NINDS Section of Infections of the Nervous System**

# Objectives

- Describe the definition and criteria for encephalitis
- Discuss two common causes of viral encephalitis on the East Coast
- Examine viral persistence in the CNS
  - How viruses spread between cells in the CNS
  - How viruses evade the immune system
  - How viruses form reservoirs





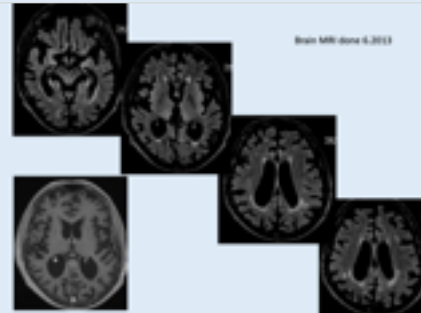
## Rare Mosquito-Borne Jamestown Canyon Virus Detected in New Hampshire

By CASEY MCDERMOTT • AUG 18, 2017

# Case Presentation

## Case Presentation

- 44 yr old former computer programmer
- 2009: imbalance, dysarthria
- Involuntary movements (dystonia, chorea)
- Cognitive dysfunction- subcortical dementia by 2013

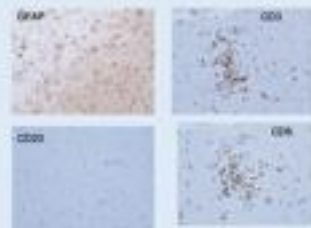


## Intrathecal Synthesis of Antibodies

Date	WBC (cells/mm <sup>3</sup> )	WBC (cells/mm <sup>3</sup> )	Protein (mg/dL)	Glucose (mg/dL)	CSF IgG (mg/dL)	CSF IgG (mg/dL)	CSF IgG (mg/dL)	CSF IgG (mg/dL)
Baseline	45	0	15-45	40-70	< 1000 µg/dL	undetectable	0.26 (0.42)	<0.1
Day 1	0	18	82	58	normal	antibodies	<b>3.74</b>	<b>99.1</b>
Day 14	0	18	71	58	not tested	not tested	<b>5.65</b>	<b>102</b>

Extensive work up for infections including PCR for arboviruses in CSF was negative

## Brain Biopsy



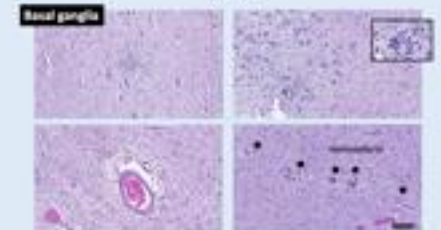
## Treatment

IV STEROIDS 1 g x 3 days  
Large volume spinal tap  
IV Ig 5 day course  
Sinemet  
EDTA chelation for mercury  
Plasmapheresis  
Cyclophosphamide

No observable benefit.

Died in June 2014

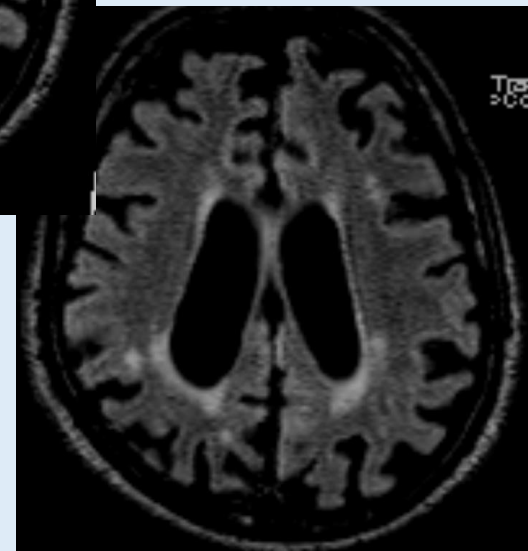
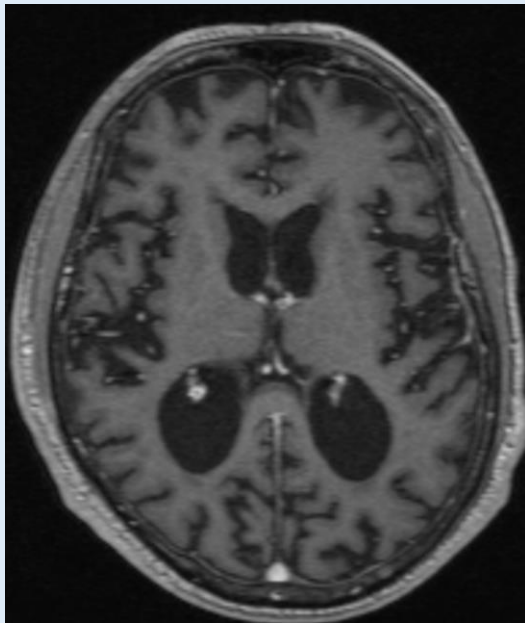
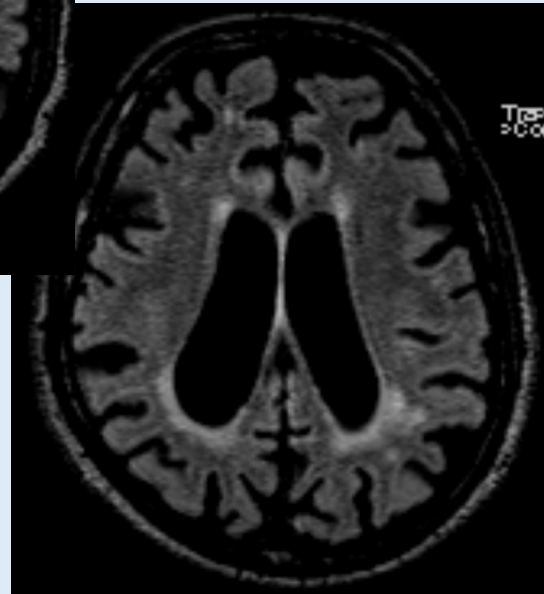
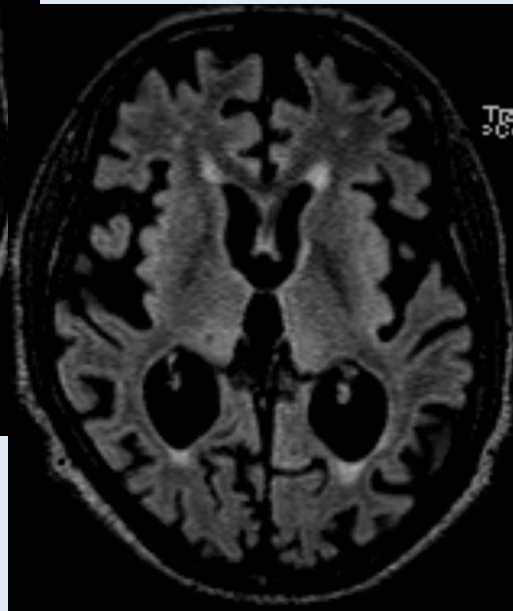
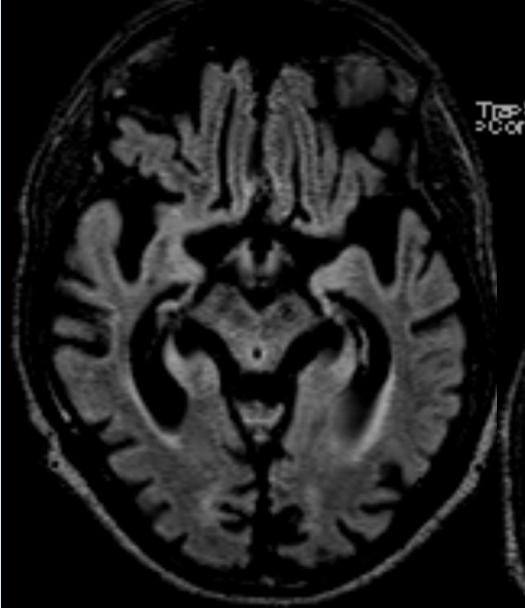
## AUTOPSY



# Case Presentation

- 44 yr old former computer programmer
- 2009: Imbalance, dysarthria
- Involuntary movements (dystonia, chorea)
- Cognitive dysfunction- subcortical dementia by 2013

Brain MRI done 6.2013



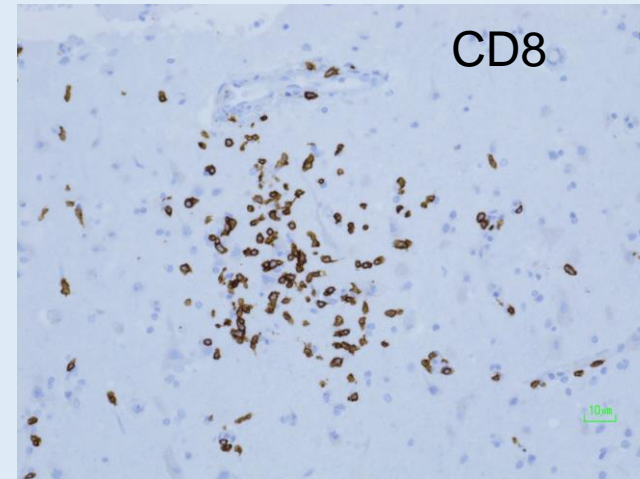
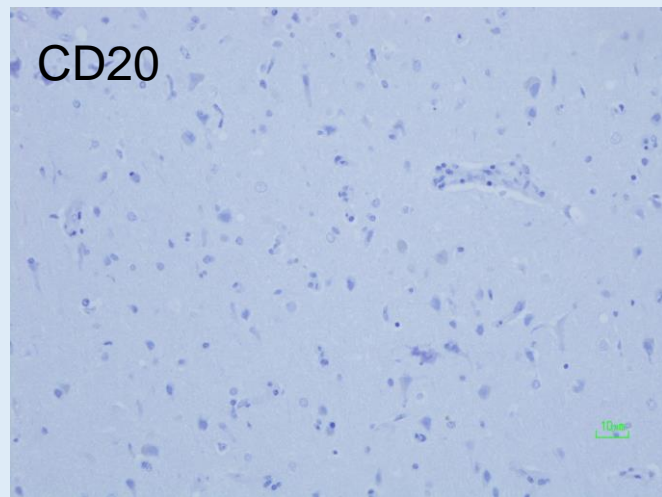
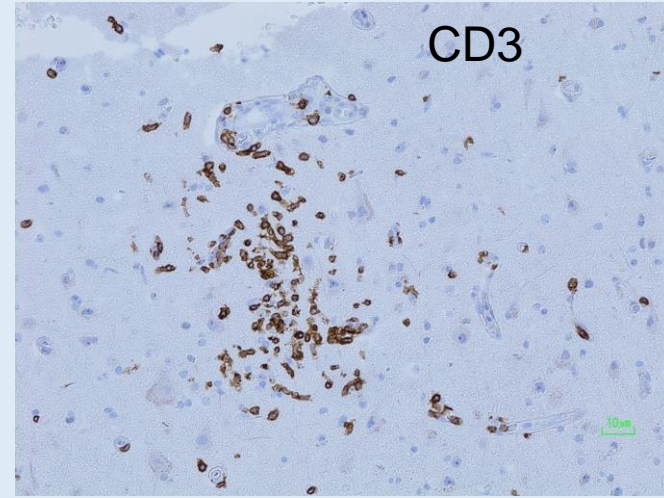
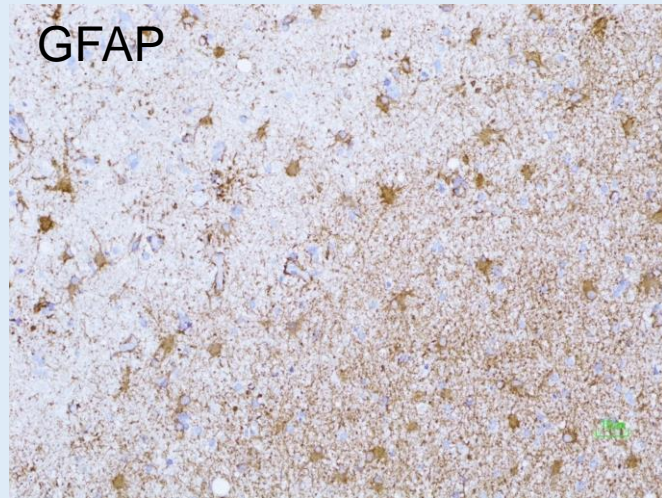
## Intrathecal Synthesis of Antibodies

Date	WBC (cells/mm <sup>3</sup> )	RBC (cells/mm <sup>3</sup> )	Protein (mg/dL)	Glucose (mg/dL)	Total Tau* (pg/mL)	14-3-3 protein*	IgG index	IgG synthesis (mg/dL)	Oligoclonal bands
Normal ranges	<5	0	15-45	40-70	< 1150 pg/mL	undetected	0.26- 0.62	<8	0
Jun- 2013	3	18	81	58	normal	ambiguous	<b>3.74</b>	<b>93.1</b>	<b>15</b>
May- 2014	2	18	71	59	not tested	not tested	<b>5.65</b>	<b>102</b>	<b>17</b>

Extensive work up for infections including PCR for arboviruses in CSF was negative



# Brain Biopsy





# Treatment

IV STEROIDS 1 g x 3 days

Large volume spinal tap

IV Ig 5 day course

Sinemet

EDTA chelation for mercury

Plasmapheresis

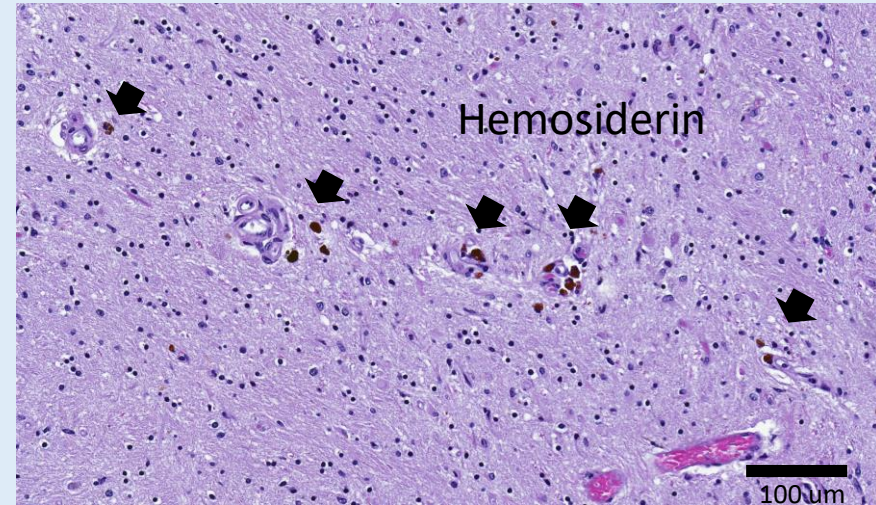
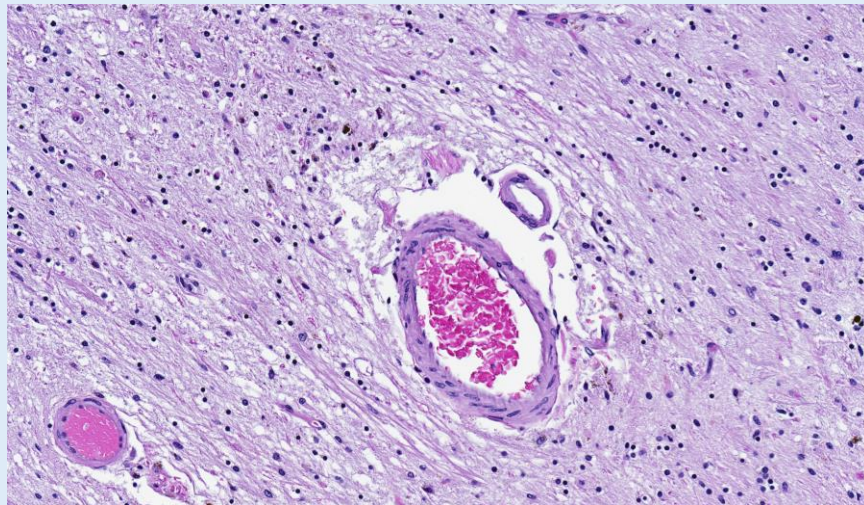
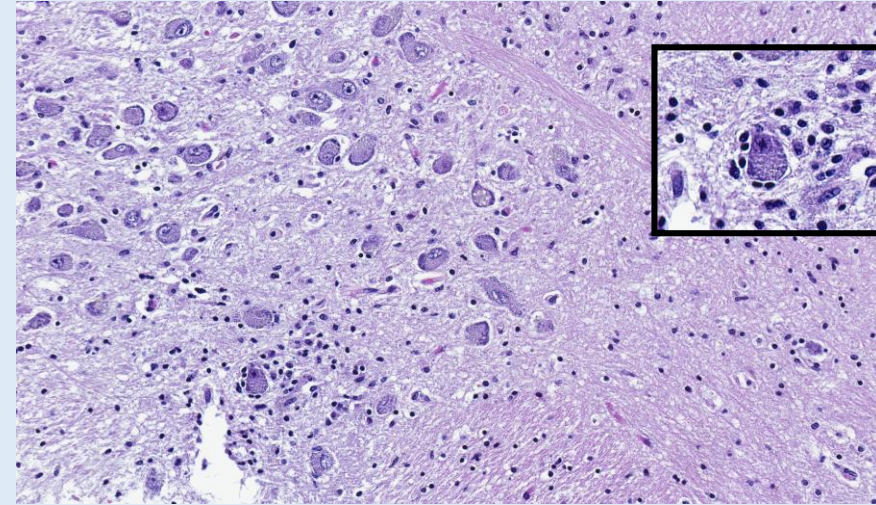
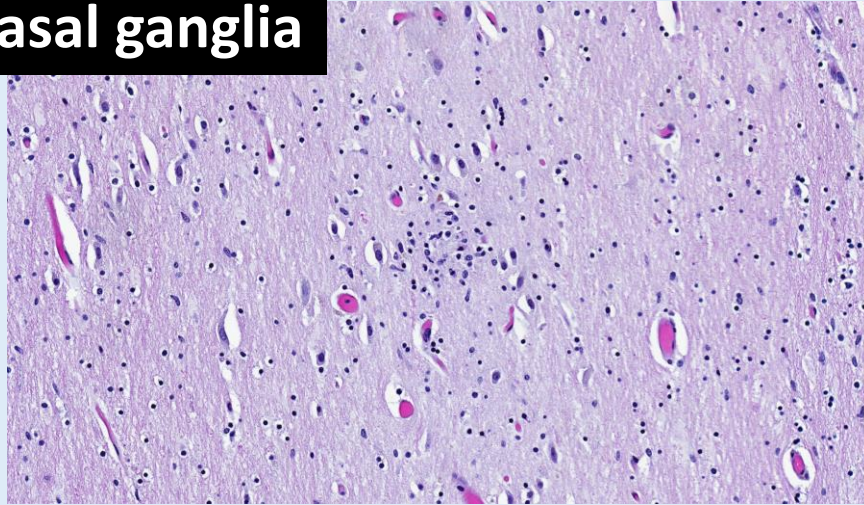
Cyclophosphamide

No observable benefit.

Died in June 2014

# AUTOPSY

## Basal ganglia



# Encephalitis

## Pathologic definition

Inflammation of brain parenchyma caused by infection or autoimmunity

## Clinical Definition

Altered mental status lasting >24 hours with no alternative cause identified

Supportive features

- Fever

- Seizures

- Focal neurologic deficit

- CSF pleocytosis

- Abnormal neuroimaging consistent with encephalitis

- Abnormal EEG consistent with encephalitis



# Encephalitis

## What is not encephalitis?

Toxic exposures

Systemic infections

Metabolic derangements

Cerebrovascular disease

# Diagnostic Approach

## History

Travel  
Exposures  
Outdoor activities  
Existing medical problems

## Lab

Blood cultures  
HIV testing  
LP with opening pressure  
Neuroimaging

## Physical Exam

Neurologic localization  
Cranial nerves and abnormal movements

# Diagnostic Clues: A Sample

## Travel to Asia

Japanese encephalitis virus

Dengue

Malaria

Nipah virus

## Immunocompromised

CMV

HHV6/7

Toxoplasma gondii

Tuberculosis

Fungal infections

WNV

## Cat bite

Bartonella, especially with seizures



# Viral Encephalitis

## Acute

**Arboviruses**

**Herpes viruses**

**Enteroviruses**

Filoviruses (Ebola/Marburg)

Rhabdoviruses (Rabies)

Paramyxoviruses (Measles)

Arenaviruses

Bunyaviruses

Rubella

Rotavirus

Influenza

## Subacute

HIV

Polyoma viruses (JCV, BK)

SSPE

No cause found

60-70%.

## Causes of specific viral encephalitis syndromes

Limbic encephalitis	Cerebellar	Parkinsonism	Rhombencephalitis	Encephalomyelitis
HSV-1	VZV	JEV	Listeria	WNV
	EBV	WNV	WNV	EV71
HHV-6	Paraneoplastic	St. Louis	JEV	JEV
	St. Louis	Nipah	EV71	Tick-borne encephalitis
			TB	Zika
				Rabies
	Mumps			VZV
				HSV
				CMV
				EBV

Modified from Cho and McKendall, Handbook of Clinical Neurology 2014

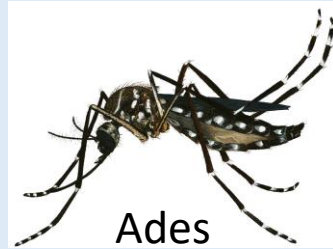
# Arboviruses

## Mosquitoes

Zika  
Dengue  
Chikungunya  
Yellow fever  
**West Nile**  
Japanese B encephalitis

St Louis  
**Eastern Equine**  
Western Equine  
Venezuelan Equine  
Usutu

La Crosse  
Murray Valley encephalitis  
Cache Valley  
Jamestown Canyon



## Ticks

Powassan  
Colorado tick fever  
Tick-borne encephalitis



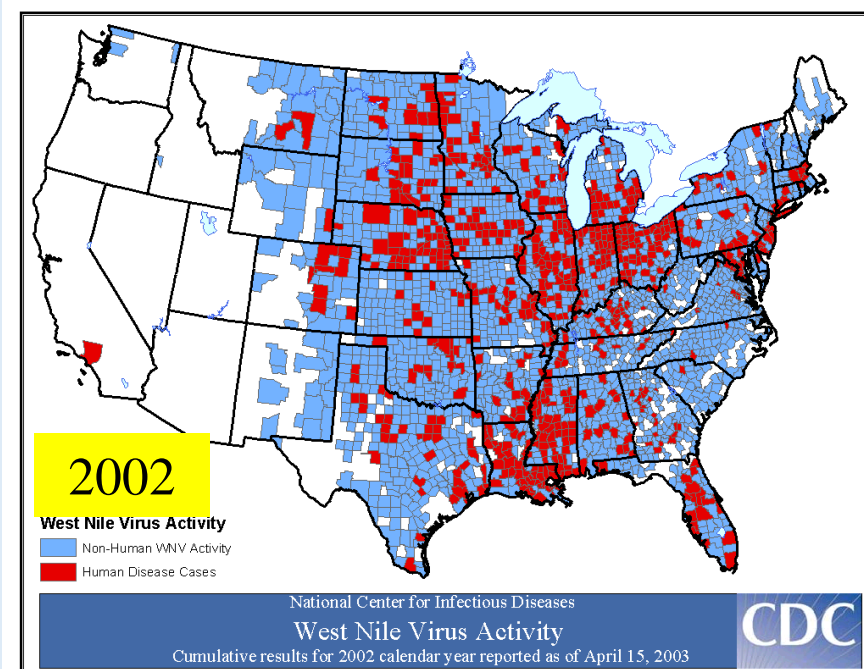
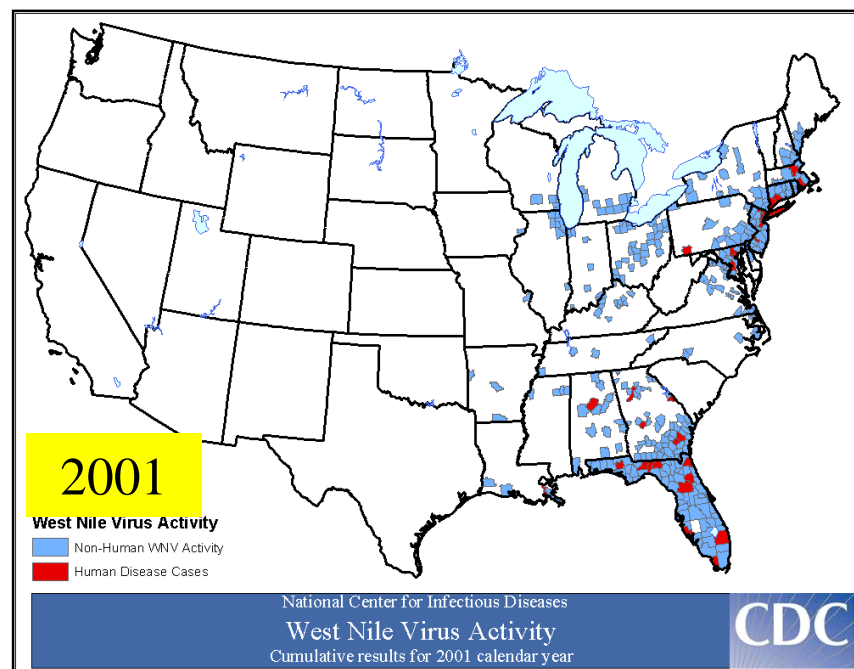
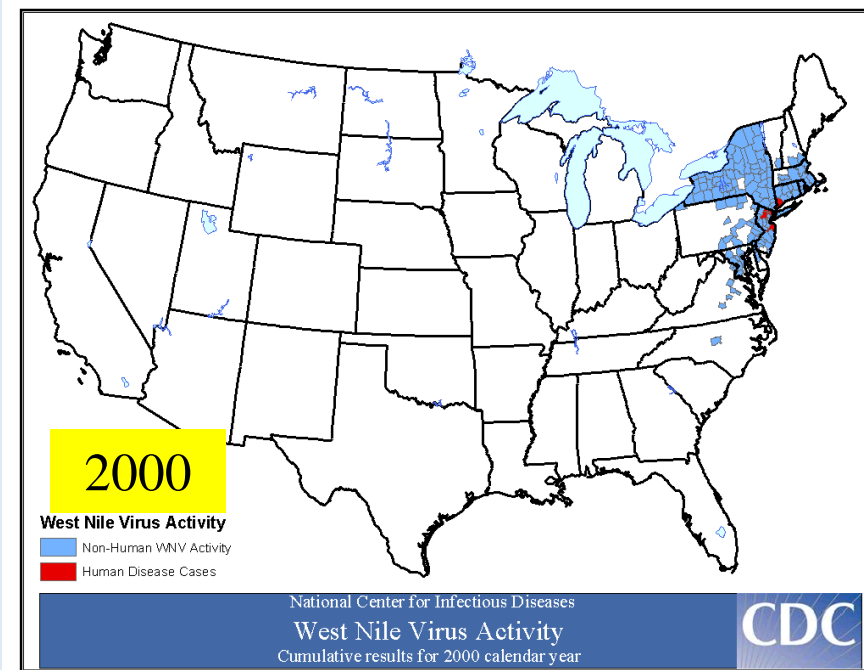
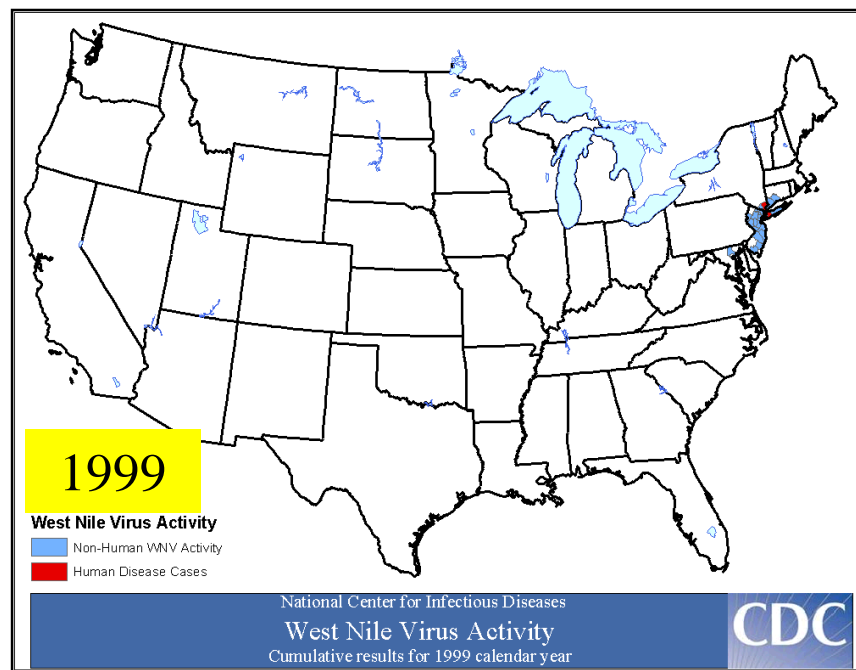
Male

Female

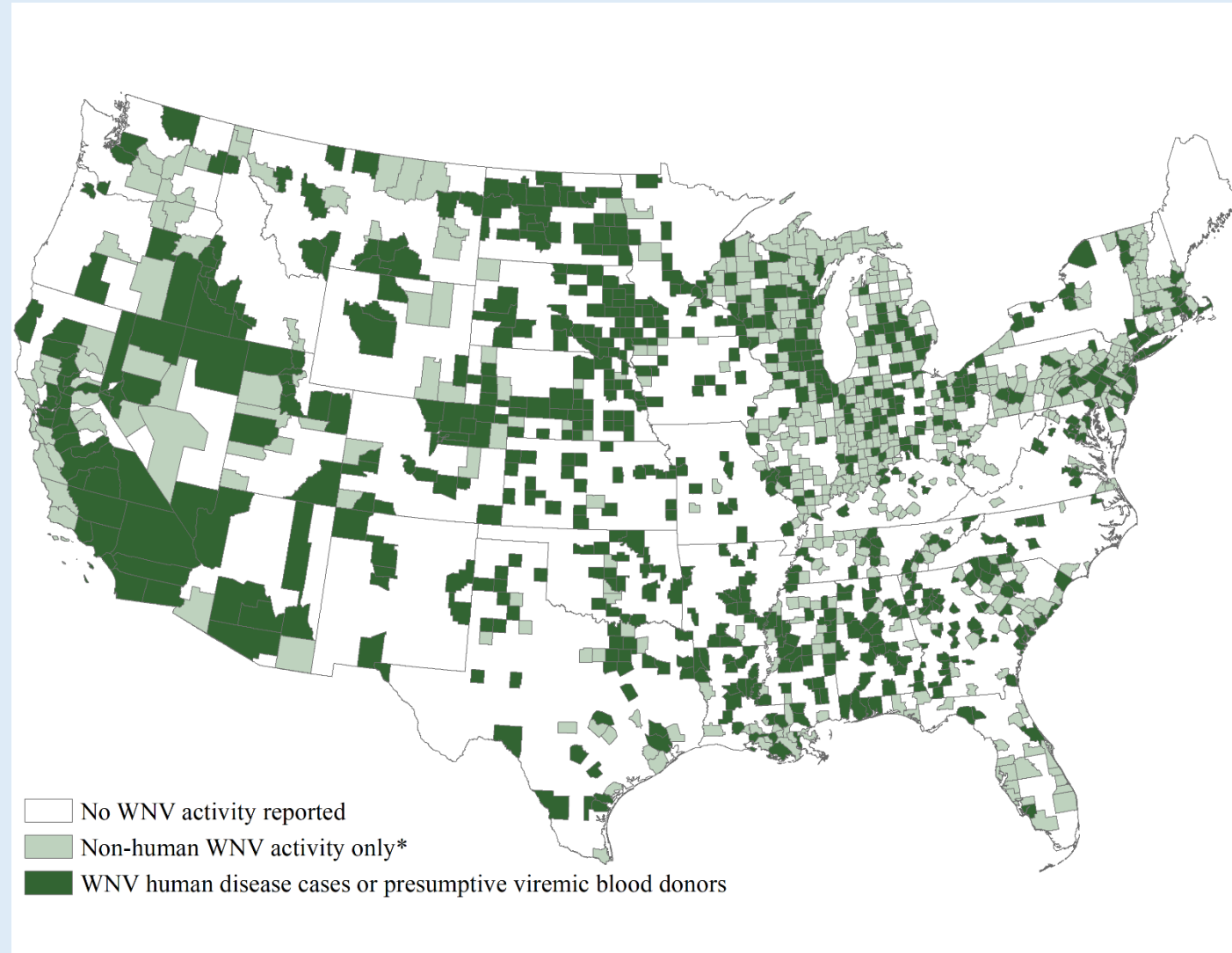


# West Nile Virus Epidemiology

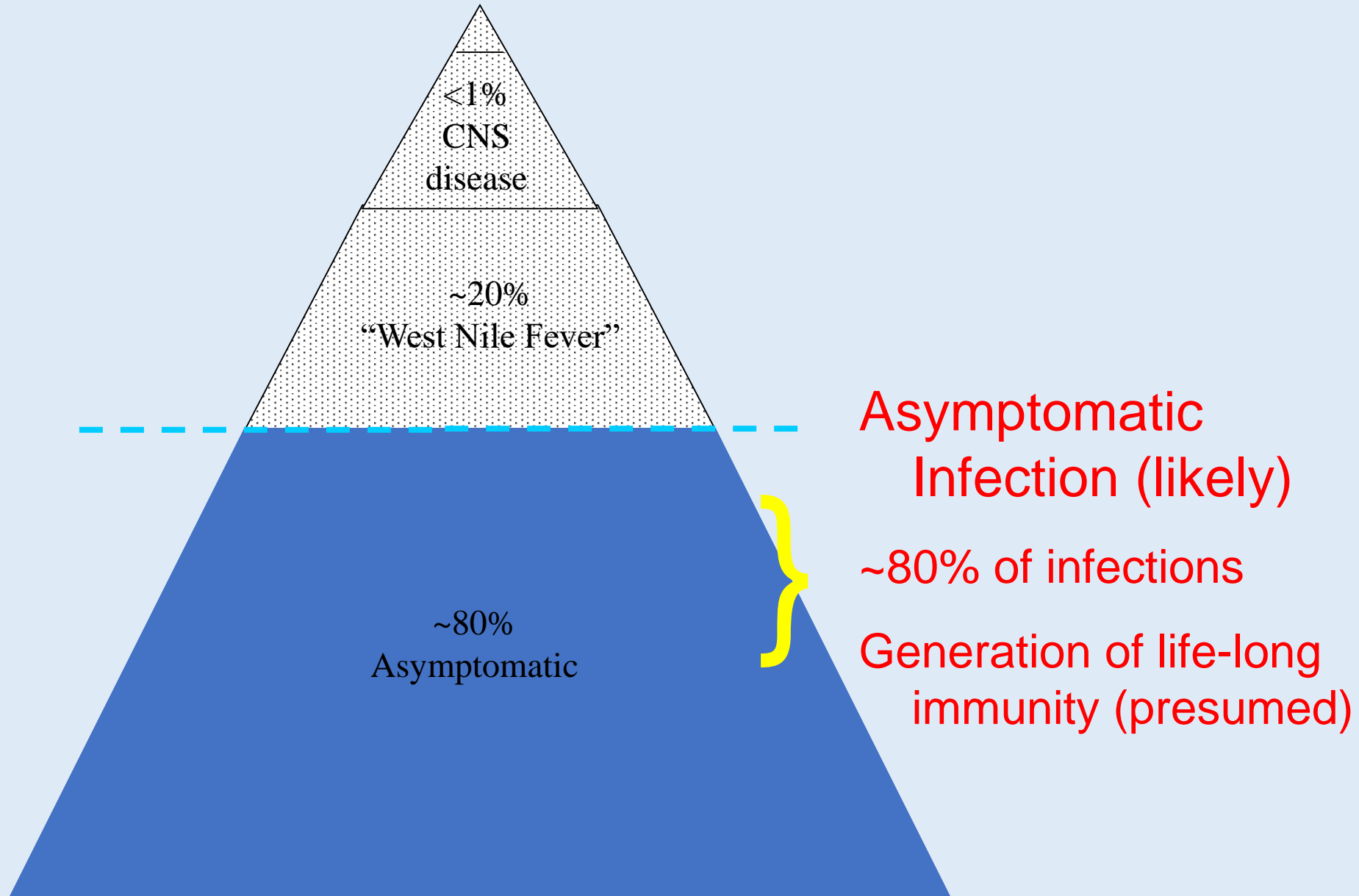
- Isolation in 1937, West Nile district of Uganda
- HISTORICALLY (e.g., prior to 1996):
  - Infrequent outbreaks
  - Mild, dengue fever-like illness
  - CNS involvement rare
  - Wide distribution throughout Asia, Eastern Europe, Africa



# WNV Activity, 2017

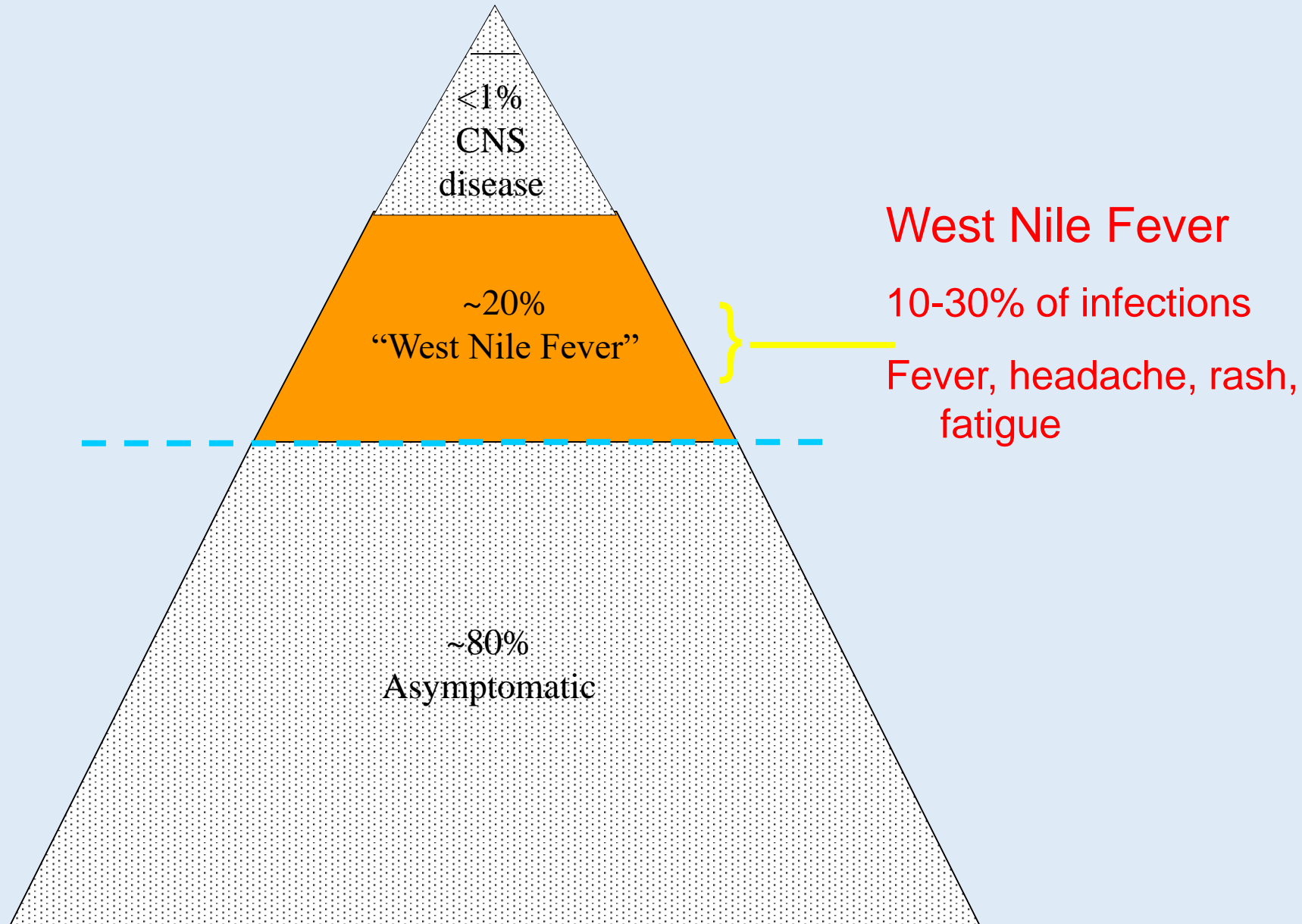


# WNV Human Infection “Iceberg”

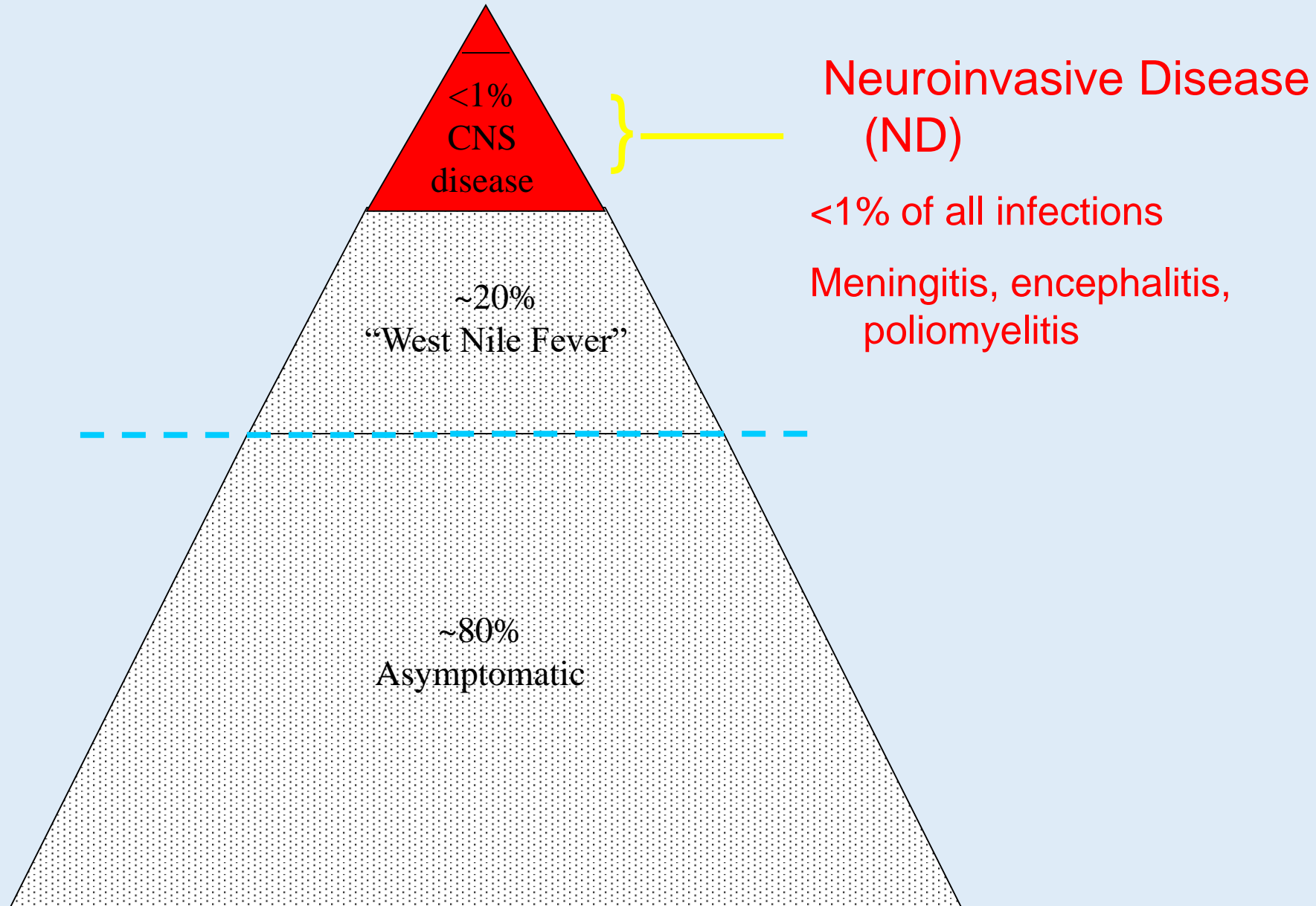




# WNV Human Infection “Iceberg”



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# Clinical Manifestations of WNV

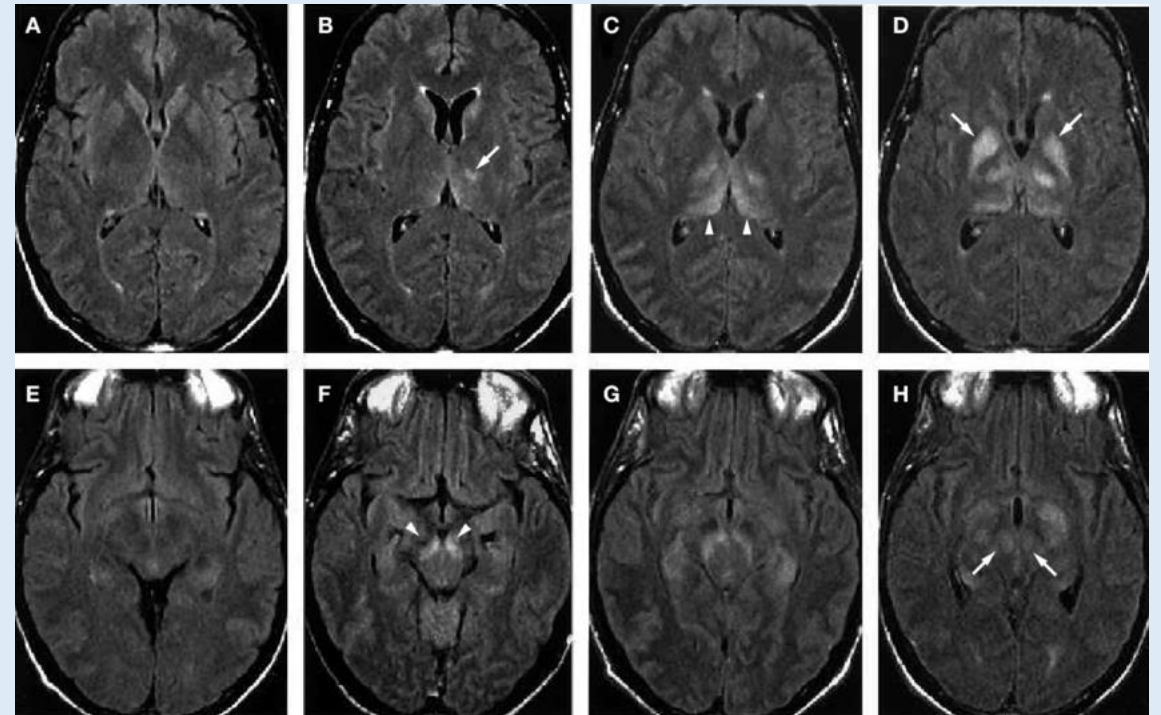
Meningitis (fever,  
headache, vomiting)

Altered mental status

Movement disorders (25%)

Cranial nerve deficits (10%)

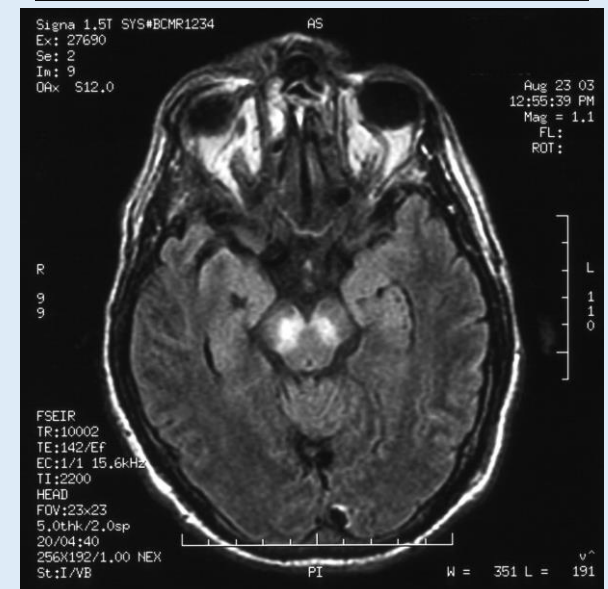
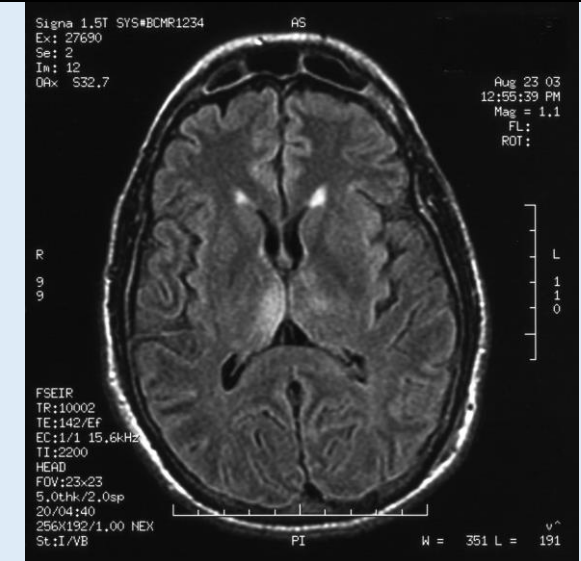
Anterior Myelitis



# WNV and Movement Disorders

- Tremor
  - Sometimes associated with other viral infections
  - Coarse; postural / kinetic
  - Occasionally functionally impairing
- Myoclonus
  - Quick, uncontrolled muscle twitching
  - Upper extremities, face
  - Bothersome to patients
- Parkinsonism
  - “Cogwheel” rigidity, bradykinesia, postural instability
  - Functionally impairing
- OUTCOMES: WNV = 15-20%

Sejvar et al. JAMA 2003



# WNV “Poliomyelitis”

- Involvement of anterior horn cells-- acute, asymmetric paralysis (generally no sensory loss)
- Relatively infrequent - ~12% of cases of WNV
- May be younger in age, previously healthy





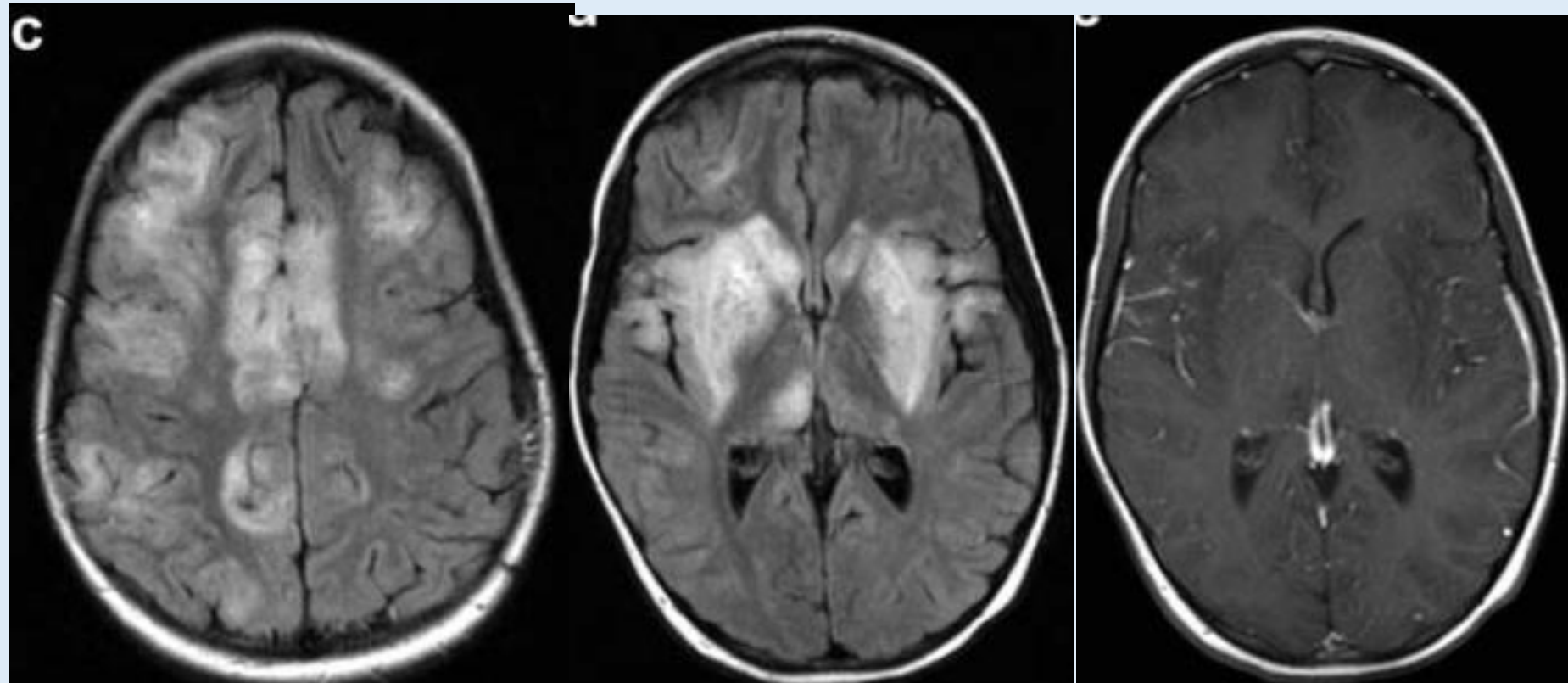
# Case (Lury et al., Emerg Rad 2004)

8 yr girl in (Florida)

(August): Fever, sore throat, seizures x 4 days

Decreased level of consciousness

CSF: 56 neutrophils; 31 Lymphs; 7 monocytes



# Eastern Equine Encephalitis: Key points

IgM positive

Most destructive of all arboviruses with necrotic lesions

Spinal cord is spared

Risk Factors

- Children

- Immunotherapy (rituximab)

High mutation rate because no proof reading of RNA

Spread by mosquitos, can infect birds

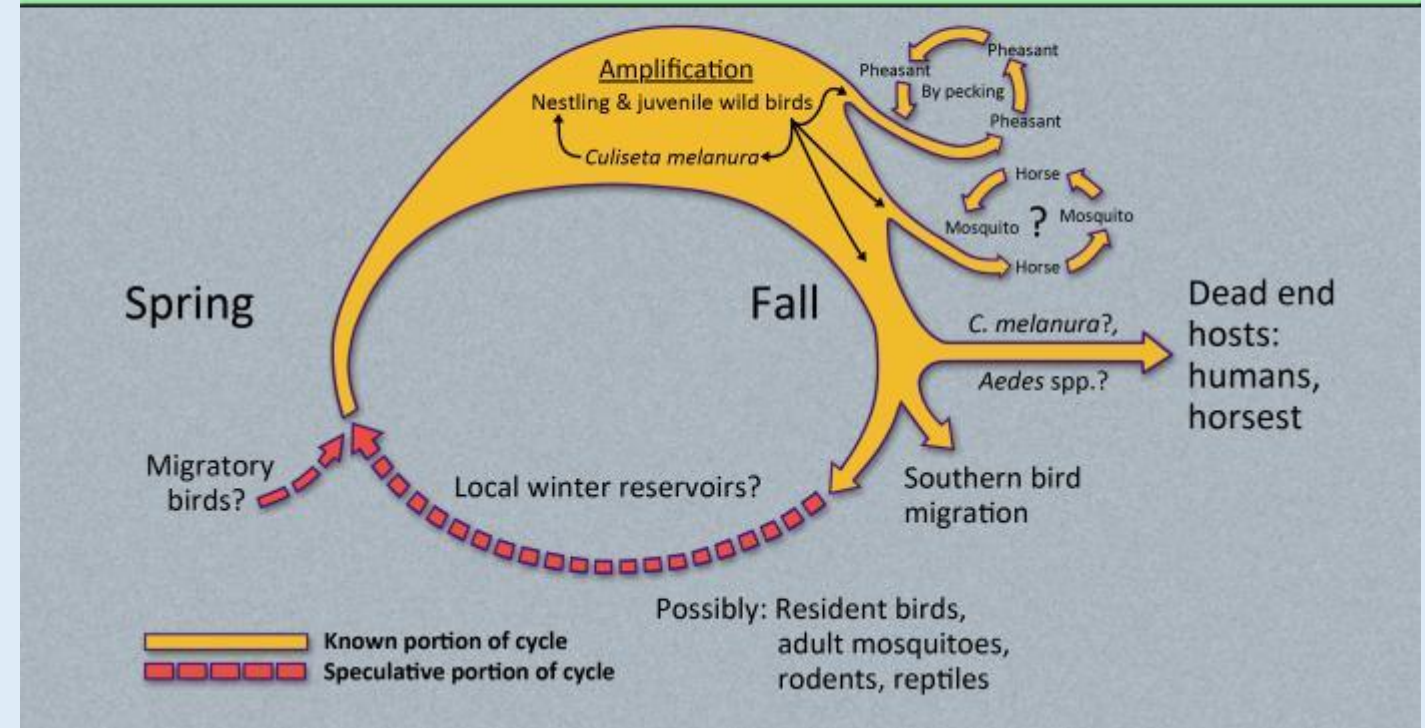
# Eastern Equine Encephalitis (EEE) Epidemiology



Methuen, MA

- 2019: Seven deaths reported
  - Virus found Maine to Alabama

## Eastern Equine Encephalitis Virus (EEEV) Cycle in the U.S.



# **A case of immunotherapy-responsive eastern equine encephalitis with diffusion-weighted imaging**

420 NEUROLOGY 56 February (1 of 2) 2001

*M.R. Golomb, MD; M.L. Durand, MD; P.W. Schaefer, MD;  
C.T. McDonald, MD; M. Maia, PhD; and L.H. Schwamm, MD*



neurocritical  
care  
society

Neurocrit Care (2013) 19:111–115

DOI 10.1007/s12028-013-9822-5

## **PRACTICAL PEARL**

# **Successful Management of Severe Neuroinvasive Eastern Equine Encephalitis**

Linda C. Wendell • N. Stevenson Potter •  
Julie L. Roth • Stephen P. Salloway •  
Bradford B. Thompson

# Treatment

Raised intracranial pressure (aggressive management)

- IV steroids

- shunt

- mannitol (?)

Seizures (status epilepticus)

IVIG (give early)

- neutralization of virus by preventing viral entry to cells

- clearance of virus from infected neurons

- cytotoxic T cells are not effective in clearing virus from neurons



# Conclusions

- There is an unprecedented increase in arboviral infections worldwide
- Neurological Complications are the most dreaded manifestations
  - Involves the entire neuro-axis
  - The young and elderly are the most vulnerable
  - Manifestations can be acute or subacute
  - Diagnosis can be challenging
- No antiviral drugs are currently available